Support for new claims 83 and 84 may be found in originally filed claims 1, 3, and 8.

Support for new claims 85 and 95 may be found in originally filed claim 41.

Support for new claims 86 and 96 may be found in originally filed claim 42.

Support for new claim 87 may be found in originally filed claim 12.

Support for new claim 88 may be found in originally filed claims 19, 26, 27, and 28.

Support for new claim 89 may be found in originally filed claim 29.

Support for new claim 90 may be found in originally filed claim 30.

Support for new claims 91, 92, and 93 may be found in originally filed claim 32.

Support for new claim 94 may be found in originally filed claim 40.

New claims 79-96 are supported by the specification as originally filed. Accordingly, they do not involve new matter and entry of them is respectfully requested.

Applicants thank Examiners Gambel and Adams for the courtesy of an interview on October 24, 1996. The following provides a more full discussion of the issues in the October 24 interview.

APPLICANTS' INVENTION

The claimed invention is directed to methods for using soluble B7 or CD28 fusion proteins. Applicants' invention involves the discovery that blocking the CD28/CTLA4/B7 pathways result in the inhibition of T cell proliferation. In accordance with this discovery, the claims recite the use of soluble B7 and CD28 fusion proteins.

REJECTION NOT BASED ON THE PRIOR ART

The Examiner rejected claims 1, 3, 41, and 42 under 35 U.S.C. §112, first paragraph for reasons of record. Applicants respectfully traverse the rejection as follows.

It is uncontroverted that the specification is enabling for the use of B7Ig or CD28Ig in a method for inhibiting T cell proliferation (Office Action at page 2, lines 16-17).

The controversy lies in whether the specification is enabling for the use of soluble B7 fusion proteins or soluble CD28 fusion proteins in a method for inhibiting T cell proliferation (Office Action at page 2, lines 20-31).

Applicants are entitled to more than the use of B7Ig and CD28Ig. The invention is directed to the discovery that B7 will recognize CD28 (and vice-versa) and that this recognition produces the effects claimed. Once those skilled in the art realized applicants' discovery, it would have been well within their skill to make other soluble B7 molecules which bind CD28, or soluble CD28 molecules which bind B7, to effect the claimed methods because methods for making soluble proteins were known.

Applicants respectfully contend that the specification is enabling for the use of soluble B7 fusion proteins and soluble CD28 fusion proteins in a method for inhibiting T cell proliferation because (1) the specification describes soluble fusion proteins and provides examples of soluble fusion proteins; and (2) soluble fusion proteins were well known before applicants' invention.

THE SPECIFICATION DESCRIBES SOLUBLE FUSION PROTEINS AND PROVIDES EXAMPLES OF SOLUBLE FUSION PROTEINS

The specification describes the use of soluble fragments of the B7 or CD28 to react with T and B cells, respectively (specification at page 23, lines 23-25). For example, in one embodiment, soluble B7 contains the extracellular domain (e.g. amino acids 1-215) of the B7 antigen (specification at page 7, lines 25-30). In another embodiment, DNA encoding amino acid residues from about position 1 to about position 134 of the sequence corresponding to the extracellular domain of the CD28 receptor is joined to DNA encoding amino acid residues of the sequences corresponding to the hinge, CH2 and CH3 regions of human Ig Cγ1 to form a CD28Ig fusion protein (specification at page 8, lines 1-6).

Further, applicants made cDNA constructs encoding soluble B7 and CD28 molecules truncated at the NH_2-terminal side of their transmembrane domains (specification at page 54, lines 26-30).

Applicants teach fragments or derivatives of B7 for use in the claimed methods. These soluble B7 molecules may be produced in recombinant form using known molecular biology techniques based on the cDNA sequence published by Freeman et al. (specification at page 12, lines 20-23). Specifically, cDNA sequences encoding the amino acid sequence corresponding to the B7 antigen or fragments or derivatives thereof can be synthesized by the polymerase

chain reaction (see U.S. Patent No. 4,683,202) using primers derived from the published sequence of the antigen (Freeman et al.) (specification at page 12, lines 24-28). These cDNA sequences can then be assembled into a eukaryotic or prokaryotic expression vector and the resulting vector can be used to direct the synthesis of the ligand for CD28 by appropriate host cells, for example COS or CHO cells (specification at page 12, lines 28-30). CD28 receptor and/or its fragments or derivatives may also be produced using recombinant methods (specification at page 12, lines 29-34).

Further, the specification as originally filed contemplated use of soluble B7 and CD28 fusion proteins as set forth in originally filed claims 18, 20, 48, 54, 64, and 65. It is well established that originally filed claims are part of the disclosure of an application. Additionally, the claimed invention encompasses the use of soluble B7 and CD28 fusion proteins in the form of B7 and CD28 fragments. As used in the specification, "fragment" means a portion of the amino acid sequence corresponding to the B7 antigen or CD28 receptor (specification at page 11, lines 25-27). For example, a fragment of the B7 antigen useful in the method of the present invention is a polypeptide containing a portion of the amino acid sequence corresponding to the extracellular portion of the B7 antigen, i.e. the DNA

encoding amino acid residues from position 1 to 215 of the sequence corresponding to the B7 antigen described by Freeman et al. (specification at page 11, lines 27-33). A fragment of the CD28 antigen that may be used is a polypeptide containing amino acid residues from about position 1 to about position 134 of the sequence corresponding to the CD28 receptor as described by Aruffo and Seed, Proc. Natl. Acad. Sci. (USA) 84:8573-8577 (1987) (specification at page 11, lines 33-35 and page 12, lines 1-2).

SOLUBLE FUSION PROTEINS WERE WELL KNOWN BEFORE APPLICANTS' INVENTION

Applicants respectfully contend that applicants need not teach what was well known in the art. Methods for making soluble proteins were well known to those skilled in the art well before applicants' invention.

Expression of soluble derivatives of cell-surface glycoproteins has been achieved for CD4, the receptor for HIV-1, using hybrid fusion molecules consisting of DNA sequences encoding portions of the extracellular domain of CD4 receptor fused to antibody domains (human immunoglobulin C gamma 1), as described by Capon et al., Nature 337:525-531 (1989) (specification at page 6, lines 14-20). Soluble fusion proteins have been made with other than

immunoglobulin molecules. One example is a fusion of a portion of the rat serotonin receptor with a glutathione S-transferase, described in Gérard et al., Neuroscience 62:721-739 (1994) (attached herewith as Exhibit 1).

Further, soluble immune mediators (e.g., cytokines or lymphokines) were well known in the art (specification at page 1, lines 7-8). It was also well known that soluble molecules such as interleukin (IL)-1 and membrane receptors involved in intercellular adhesion can provide costimulatory signals (specification at page 5, lines 27-32).

Other methods of constructing soluble proteins were also known in the art. Byrn et al., Journal of Virology, 6310:4370-4375 (1989), attached herewith as Exhibit 2, describe a soluble CD4 in which the transmembrane and cytoplasmic regions have been omitted. Smith et al., Science 238:1704-1707 (1987), attached herewith as Exhibit 3, describe a soluble CD4 created by replacing the transmembrane and cytoplasmic domains with a short linker sequence. This soluble CD4 was prepared in two forms: one construct included the natural signal sequences of CD4; the other construct had the CD4 leader replaced by the signal peptide and first 27 amino acids of the glycoprotein D of herpes simplex virus type I. Another example is Lasky et al., Science 233:209-212 (1986), attached herewith as Exhibit 4, which describes a soluble recombinant gp120,

created by joining the first 50 amino acids of glycoprotein D to amino acid 61 of gp120 and trunk hitting the entire transmembrane domain of gp120.

SUMMARY

Ig fusion proteins of CD28 and B7 and truncated versions thereof were exemplified in the specification. However, this should not limit the claimed methods to these embodiments. The number and variety of examples is irrelevant if the disclosure is enabling and sets forth the best mode contemplated. Since enablement and best mode as to the CD28 and B7 Ig fusion proteins have been established, and because methods for making soluble proteins were well known before applicants' invention, the claimed methods properly encompass the use of CD28 and B7 soluble fusion proteins as claimed. Therefore, the rejection is improper and should be withdrawn.

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TERMINAL DISCLAIMER

In response to the Examiner's rejection of the pending claims as set forth in paragraphs 23-26 of the Office Action, applicants will provide a terminal disclaimer.

No fee, other than the extension fee, is deemed necessary in connection with the filing of this response. If any fee is necessary, the Patent Office is authorized to charge any additional fee to Deposit Account No. 13-2724.

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I hereby certify that this paper is being deposited this date with the U.S. Postal Service by first class mail addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Philip C. Valdez

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